## REMARKS

Claims 1, 6, 7, 9, 10, 17-24, 26 and 27 are pending. Claims 2, 3, 4, 5, 8, 11-16 and 25 are cancelled. Claims 6 and 18-20 are withdrawn. Claims 1, 7, 9, 10, 17, 21-24, 26 and 27 stand rejected. Applicants amend claims 1 and 17, and cancel claim 10 without prejudice or disclaimer of subject matter. Applicants request entry of the amendment and reconsideration of the outstanding rejections.

Rejections under 35 USC § 112 1st ¶, enablement

Claims 1, 4, 7, 9, 10, 17, 21-24, 26 and 27 stand rejected under 35 USC § 112, first paragraph for allegedly failing to enable one skilled in the art to make and/or use the invention. The rejection is based upon the Wands factors and is summarized below. Applicants' responses to the rejections are provided therewith.

"Nature of the Invention and Breadth of Claims"

The Examiner asserts that claim 1 "encompasses the use of any gene or set of genes selected from among the 310 genes listed in Table 5. Thus the invention is broad in scope and very complex." Applicants traverse.

Applicants recognize that claim 1 does encompass many permutations of gene combinations, however, each and every gene is adequately described and is represented as a working example. The expression of each gene of Table 5, individually and collectively, has been shown to change in response to the in vivo administration of CCI-779 to patients having RCC. The specification teaches the skilled artisan myriad ways to make and use each and every marker, either alone or in various combinations. Furthermore, Table 5 is not an open-ended list, but rather it is a close-ended list of markers that have been empirically determined to modulate in PBMCs in vivo in response to CCI-779 administered to a patient. Each and every conceivable combination of markers embodied in the claims is fully enabled, as one of ordinary skill in the art can pick and chose any conceivable combination of Table 5 markers to determine an in vivo activity of CCI-779 according to the claimed method.

Applicants assert that the claims are of sufficient breadth, since they are completely supported by working examples and detailed sequences. The specification provides the skilled artisan with sufficient guidance to make and use any and all combinations of

markers provided in Table 5 in the assessment of CCI-779 activity as measured in PBMCs.

"Guidance Provided by the Specification and the Existance of Working Examples."

The Office alleges that the disclosure "on the whole appears to assert that differences in PBMC gene expression before and after drug treatment would be indicative of the in vivo effect of a drug therapy upon any given non-blood disease," (emphasis added) (page 8, last paragraph) and that "the specification does not provide a single working example [showing] the effect of the drug therapy upon the solid tumor," (office action at page 9, first paragraph.) Applicants traverse.

Applicants submit that the Office has improperly imported perceived alleged limitations from the specification into the claims (MPEP 2106.II.C and 2111.01). As stated previously, the claims do not provide for an assessment of an effect of CCI-779 therapy *upon a RCC tumor* in a patient, but rather provides for an assessment of the difference in the amount of genes, whose expression is regulated *in vivo* by CCI-779, in PBMCs obtained from an RCC patient. An *in vivo* effect of CCI-779 includes the regulation of the expression of the genes of Table 5 in PBMCs in a patient suffering from RCC. As far as guidance provided by the specification and the existence of working examples, the specification clearly teaches how to make and use the claimed invention, i.e. the procurement of PBMCs, the manufacture and detection of the markers of Table 5 (e.g., the sequences are disclosed) and the description of the patient pool. Furthermore, the biomarkers described in Table 5 were empirically derived and actually assessed from PBMCs, which were actually obtained from RCC patients, who actually received CCI-779 (working examples 1-4 of the specification.) All elements of the claims are supported and exemplified by these working examples and are thus enabled.

Should the Office persist in this rejection, Applicants respectfully ask that the Examiner provide to Applicants a scope of enablement according to MPEP 2164.04.

"State of the Prior Art and Level of Predictability in the Art."

The Office contends that predictability in this case depends upon "the correlated effects of drug therapy upon a RCC tumor and the simultaneous changes in PBMC gene expression are indicative of the in vivo activity of the drug on RCC," (emphasis added) (Office action, page 10, second paragraph.) The Office further alleges that the "claimed method proposes to use any Table 5 [marker] as a biomarker or surrogate endpoint for

the efficacy in the treatment of RCC with CCI-779 drug therapy," (Office action, page 11, paragraph 3). The Office alleges that "the art clearly teaches that the utility of a putative biomarker as a surrogate endpoint for any disease state is unpredictable and must be validated," (Office action, page 11, second paragraph.) The basis of this alleged unpredictability is the improper importation of a perceived limitation from the specification into the claims by the Office. That improper limitation is that the markers of the claimed method must serve as a surrogate endpoint for CCI-779 efficacy against RCC. However, the claims DO NOT require efficacy of CCI-779 against RCC and as such are fully supported for example in the working examples as well as the detailed description of the markers in Table 5 and in the sequence listing.

"Amount of Experimentation Necessary."

The Office alleges that "one of ordinary skill in the art would have been required to perform an undue amount of experimentation in order to accurately determine gene expression differences in PBMCs of patients with RCC before and after drug treatment, [and] then determine which of those difference were indeed indicative of the drug therapy and could therefore be used as an indication of the drug's activity in vivo. The in vivo drug activity on PBMC gene expression and upon the RCC would need to be correlated," (Office action, bottom of page 12 through top of page 13.) The Office further argues that "without a connection between the drug efficacy for the treatment of the RCC, one of ordinary skill in the art would clearly not be apprised of how to make and *use* Applicants invention," (Office action, bottom of page 13 to top of page 14.) Applicants traverse.

Applicants repeat their assertion that the Office has improperly imported a perceived limitation form the specification into the claims (see MPEP 2106 part II section C and MPEP 2111.01). The Office bases this particular argument on the allegation that the only real world use provided in the specification for the invention is the indication of the efficacy of the drug on the RCC. Respectfully, this is not the case. The specification does not narrowly limit the disclosed use of the claimed invention to determining the efficacy of the drug CCI-779 on RCC. To the contrary, the specification teaches several viable uses for the claimed method, including "providing early evidence of drug exposure in vivo" (published specification at paragraph 47), "further validating surrogate markers identified in *in vivo* studies" (published specification at paragraph 47), and monitoring "the direct effect of CCI-779 on PBMCs or other blood cells," (paragraph 416). Thus, the

currently pending claims are supported in full by the specification and working examples as to the utility of the claimed methods, which have been actually reduced to practice. No undue experimentation is required to practice the invention as claimed.

In light of the arguments presented herein, Applicants assert that the currently presented claims are enabled. Accordingly, Applicants request withdrawal of the rejection of claims 1, 7, 9, 17, 21-24 and 26-27 under 35 U.S.C. § 112, first paragraph (enablement).

Claim Objections

Claim 10 was objected to for being of improper dependent form for failing to limit the subject matter of a previous claim. Claim 10 is cancelled, rendering the objection moot.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 7, 10 and 17 stand rejected under 35 U.S.C. § 112, second paragraph for allegedly being indefinite. Since claim 10 is cancelled, the rejection of that claim is now moot. Claim 7 is amended to designate "the peripheral blood sample" as 'the peripheral blood sample of step (a)." No new matter is introduced by this amendment. Claim 17 is amended by deleting the phrase "from said patient" in reference to the "reference peripheral blood sample," thereby removing any alleged ambiguity regarding the source of the reference peripheral blood sample. No new matter is introduced by this amendment.

In view of the amendments to the claims, Applicants believe that the rejection has been obviated, and therefore request that the rejection of claims 7 and 17 under 35 U.S.C. § 112 second paragraph be withdrawn.

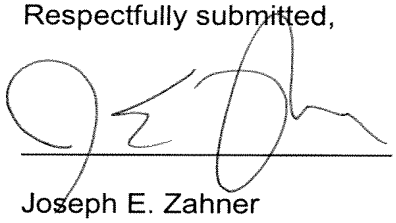
Double Patenting

Claims 1 and 10 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 21 and 34 of co-pending application, U.S. Serial No. 10/793,032. Claim 10 is cancelled, rendering this rejection against that claim moot. Applicants request that the provisional nonstatutory obviousness-type double patenting rejection of claim 1 be held in abeyance until such time that the presence of otherwise-allowable subject matter is acknowledged.

## CONCLUSION

In view of the foregoing, Applicants believe that all rejections have been overcome and claims 1, 7, 9, 17, 21-24 and 26-27 are now in a condition for allowance. The Examiner is invited to call the undersigned agent to discuss any remaining issues.

Respectfully submitted,



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